patient died. Autopsy showed a mildly atheromatous right coronary artery. The left circumflex artery terminated abruptly 3 cm distal to the bifurcation, descending as a solitary marginal artery at the anterior wall of the left ventricle. The anterior descending branch was small in caliber. There were very small atheromatous plaques lining the left circumflex and anterior descending arteries. These findings were consistent with the coronary arteriogram. Moderate hypertrophy of the left ventricle was noted. There were scattered ill-defined areas of fibrosis in the interventricular septum. The artificial pacemaker was anchored into the apex of the right ventricle. Other significant findings included incipient hilar pulmonary edema, pronounced chronic passive congestion of the liver and congestive splenomegaly.

Discussion

Many of the elements of Prinzmetal's variant of angina pectoris were present in the case here reported. The cyclic nature of the pain and the observations that it was of long standing, was not associated with exercise and that ST elevation was concomitant with it were all typical of Prinzmetal's variant. Abnormalities of rhythm and conduction are characteristic of the syndrome and this patient had, at various times, recurrent ventricular tachycardia, atrial fibrillation, complete heart block with idioventricular rhythm, and recurrent ventricular asystole.

This case was of special interest in two respects. First, there was the correlation of pathological findings with the clinical data. Prinzmetal[3] noted decided narrowing of a major coronary artery in three cases, and he suggested that the variant of angina pectoris was associated with 80 per cent or greater occlusion of one of the three major vessels. The patient described here had only mild atherosclerosis of the right coronary artery. The striking abnormality was the small size of the entire left coronary system, particularly the circumflex artery. Yet the patient had done well for almost 40 years. It would appear that the development of relatively mild coronary atherosclerosis resulted in sufficient impairment of myocardial blood flow to cause angina pectoris and congestive heart failure.

The second point of interest concerned the periods of ventricular asystole which were associated with chest pain. These episodes of cardiac arrest were the reason for implantation of an artificial pacemaker. As was expected, the chest pain was not relieved by this procedure. In fact, the severity of the pain was frequently greater after the operation. It is probable that the artificial pacemaker, by preventing asystole and unconsciousness, provided the basis for the extraordinarily intense pain. In the terminal stage, although the artificial pacemaker functioned well, the myocardium failed and could not sustain life.

Summary

Prinzmetal's variant of angina pectoris was observed in a patient who did not have severe coronary atherosclerosis. The case demonstrated an extremely unusual indication for an artificial pacemaker: Although the patient's basic cardiac rhythm was normal sinus, she was subject to bouts of ventricular asystole in association with angina pectoris, and a pacemaker was implanted for that reason.

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Latent Cerebral Vascular Insufficiency Masked by Long-Term Anticoagulant Drug Therapy

Appearance of Transitory Ischemic Attacks When Drugs Discontinued

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TWELVE YEARS AGO, Millikan, Siekert and Shick[10] reported that anticoagulant drugs stopped characteristic cerebral ischemic attacks in seven patients with intermittent insufficiency of the carotid artery. In a later report they concluded that this therapy was associated with a reduction in subsequent cere-

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bral infarction.[12] Many, if not most, clinicians agree with these conclusions,[4,6,8,9,14] but there are others who disagree.[2,3,11,13]

Further studies on groups of treated versus controlled patients with cerebral ischemic attacks have been considered either inadequately controlled or too small in numbers. Reduction of attacks in the treated groups during treatment and resumption of attacks on withdrawal of the drug has not been regarded as crucially significant. The lack of any practical objective method for measuring the hemodynamic effectiveness of treatment, plus the occasional tendency for repeated attacks to stop spontaneously has led to considerable skepticism.[2,3]

In the presence of such disagreement, all clinical relationships must be carefully studied. Under certain conditions prolonged control studies are not necessary to establish the efficacy of a therapeutic measure.

Hill[5] says that if the results "are dramatic in the light of all past experience," the period of trial need not be prolonged.

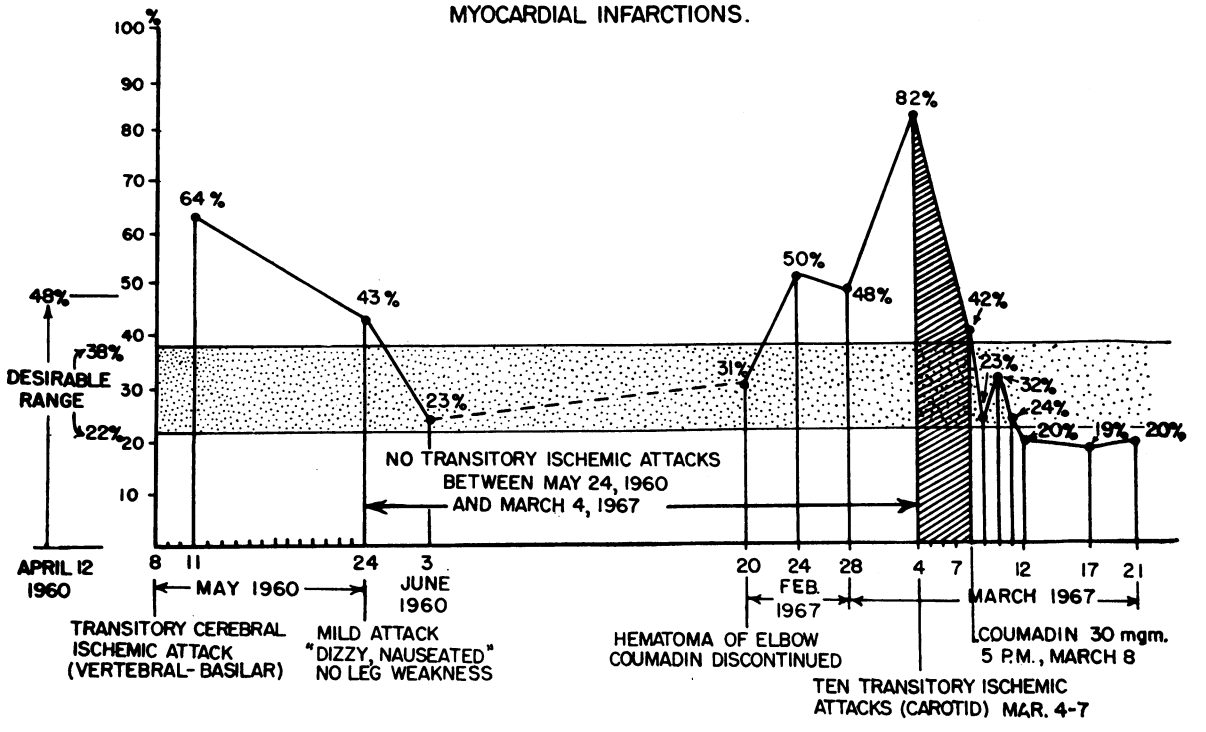
We wish to report the occurrence of transitory ischemic attacks in a patient on two occasions when long-term anticoagulant protection was removed, and the immediate cessation of attacks when anticoagulant control was resumed. On the first occasion the prothrombin level had risen inexplicably to 64 percent (see chart). The second series of attacks occurred more than six years later when warfarin (Coumadin®) therapy was discontinued because of bleeding into the right olecranon bursa. Within two weeks after the discontinuance of the drug, ten attacks of transitory cerebral ischemia occurred over a period of four days. When Coumadin therapy was resumed, the attacks ceased abruptly. In the succeeding five months there were no further attacks.

Report of a Case

The patient, a man, was first seen in 1951 at the age of 54. His weight was 221 pounds and his blood pressure was 164/104 mm of mercury. His mother had died at age 68 of "a stroke" after repeated syncopal attacks. In March 1951 the patient had severe precordial pain and an electrocardiogram tracing was typical of diaphragmatic myocardial infarction. He was given ethyl biscoumacetate (Tromexan®). Later Coumadin was substituted and continued for long-term therapy.

In January 1958 the blood pressure was 172/122 mm of mercury. A month after chlorothiazide

TRANSITORY CEREBRAL ISCHEMIC ATTACKS UNMASKED WHEN PROTHROMBIN LEVELS SUDDENLY ELEVATED. PATIENT ON LONG TERM THERAPY FOLLOWING MYOCARDIAL INFARCTIONS.



(Diuril®) was prescribed it was 144/98 mm. Since then the blood pressure has been controlled except for occasional diastolic pressure measurements over 100 mm. On 8 May 1960, after dinner which included a crab cocktail and a highly seasoned salad, the patient "became dizzy, things went around, my legs felt weak." Thinking that the dinner had caused these symptoms, he took some soda and vomited. In a few minutes he felt all right. Two days later he came to the office. At that time the prothrombin level was 64 per cent. On 24 May he had a mild episode characterized by dizziness and nausea but without weakness of the lower limbs. The prothrombin level was 43 per cent. A neurologist examined him and reported: "The patient suffers from intermittent episodes of basilar artery insufficiency, characterized by vertigo, nausea, nystagmus and weakness of the lower extremities. I should strongly advise his present program of anticoagulation be continued indefinitely." Coumadin therapy was continued.

During the ensuing six years he had few untoward symptoms. He made a trip to Europe and traveled widely throughout this country. On 26 December 1965 he came to the office complaining of a "solid" pain of moderate severity over the lower sternum. An electrocardiogram showed the old evidence of diaphragmatic infarction and also ST-T changes indicative of acute anterolateral myocardial infarction. The prothrombin time was: Control, 14.5 seconds; patient, 27 seconds. Within three months the patient was walking on level places without difficulty.

Following treatment for an episode of acute dyspnea and pulmonary edema on 15 April 1966, he improved rapidly and was soon active and asymptomatic. The use of Coumadin was continued throughout the two attacks of coronary occlusion and the one of acute left ventricular failure. in the course of a routine monthly test on 24 January 1967 the prothrombin times were 15 seconds for the control and 31 seconds for the patient. The dosage of Coumadin was reduced.

On the morning of 20 February 1967 while the patient was walking his dog, his right elbow suddenly swelled until it was the size of a lemon. He was seen at the office where a diagnosis of hematoma of the olecranon bursa was made. At that time the control prothrombin time was 12 seconds, the patient's 18 seconds. Because of the relatively large hematoma, the use of Coumadin was discontinued for the first time in 16 years. Twelve days after the use of Coumadin had been discontinued, his sister-in-law called and said that, while the patient was standing, weakness developed suddenly in the left leg and he had difficulty walking to a chair. When he sat down, he attempted to cross his left leg over his right, but was unable to do so. She said the left side of his mouth drooped and the left side of his face sagged. A few minutes later she called back and said he had totally recovered.

He was admitted to St. Vincent's Hospital where prothrombin time tests indicated the control value to be 14 seconds, the patient's 15 seconds. He was seen by a neurologist who reported: "I saw the patient on March 4 and 5. During the second visit, he had a paretic episode involving the left upper limb and associated with mental confusion. Within a matter of minutes, he had recovered but for slight difficulty elevating the arm to the vertical plane." Two other episodes were observed by a nurse on 5 March. On 6 March the nurse's notes were: "12:45 p.m., difficult to move left forearm. Lasted 3 minutes. 1:05 p.m., confused. Unable to move left hand. 4:00 p.m., awakened confused. Left arm weak, less than 45 minutes, then became normal. 10:30 p.m., weakness in left side. Mental confusion."

When the house physician arrived 10 minutes after the nurse's 10:30 note, the patient was "rational, moving his arm well."

The next day the nurse wrote: "1:00 p.m., confused. Weak arm and leg, lasting a few minutes. 4:00 p.m., confusion and weakness, lasting two minutes."

Thus, in the course of four days, ten transitory cerebral ischemic attacks involving the right internal carotid system had been noted. In the course of consultations with a neurologist and an orthopedist, it was agreed the risk of allowing the episodes of cerebral insufficiency to continue was worse than the risk of further bleeding into the bursa. The orthopedist believed that the hemorrhage was not spontaneous but that the patient had inadvertently bumped or otherwise traumatized the elbow. The arm was bandaged firmly and 30 mg of Coumadin was given. From that time on, the special nurses noted no additional episodes. No further bleeding occurred into the bursa. On the following day the control prothrombin time was 14 seconds, the patient's 20 seconds. On 9 March the prothrombin time was: control, 14 seconds; patient's, 27 seconds. The patient was dis-

charged on 11 March and at the time of last report (August 1967) has had no further episodes.

Discussion

The progressive nature of clinical atherosclerotic disease, with involvement first of the coronary and then the cerebral arteries, was demonstrated in the present case. The appearance of repeated attacks of transitory cerebral ischemia relatively soon after the anticoagulant drug was stopped, and their abrupt cessation when administration was resumed was striking. A similar abrupt cessation of attacks within 48 hours of administration of Tromexin® and dicumarol was described in Millikan, Siekert and Shick's Case No. 1.

The exact mechanism of action of Coumadin or Coumadin-like drugs in relieving transitory ischemia is not clear. The natural history in any one patient is unpredictable. Cerebral ischemia is dependent on the interplay of so many variable factors that the control of a single factor could not be expected to benefit all patients. In Marshall's study of 158 patients with transitory ischemic attacks who had no anticoagulant treatment, 90 (57 per cent) had no cerebral transitory ischemic attacks during the subsequent five years they were observed.[6,7] It was impossible to predict which patients would have infarction. However, three-fourths of those in whom cerebral infarction developed following an ischemic attack in the carotid system, had had only one or two such attacks before the completed stroke. The chief risk of treatment, that of cerebral hemorrhage, occurs mainly in those with hypertension or with already established but unrecognized bleeding, as from an oozing berry aneurysm.[1] In the non-hypertensive patient the risk of cerebral infarction would seem greater than the risk of cerebral hemorrhage.

It is concluded that the possibility of a chance relationship explaining the cessation of attacks following the reinstitution of anticoagulant drug therapy would seem exceedingly remote in the case reported.

Anticoagulant drug therapy, prescribed for coronary artery insufficiency, apparently was of additive although unrecognized value in relieving cerebral artery insufficiency.

Summary

Transitory cerebral ischemic attacks occurred on two occasions in a patient on long-term anticoagulant drug therapy following myocardial infarction. The first attack developed when the Coumadin drug effect was reduced. The apparent protective action of the anticoagulant drug was disclosed when the drug was discontinued because of bleeding. Ten attacks then occurred in four days.

The abrupt cessation of attacks when Coumadin was readministered indicated that an underlying, previously unrecognized cerebral vascular insufficiency had been concealed by anticoagulant drug treatment, and was unmasked when the drug was stopped.

Generic and Trade Names of Drugs

Warfarin—*Coumadin.*®
Ethyl biscoumacetate—*Tromexan.*®
Chlorothiazide—*Diuril.*®

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